EFFICACY OF VIRGIN COCONUT OIL SUPPLEMENTED-MILK FEEDING IN AUGMENTING WEIGHT GAIN AMONG VERY LOW BIRTH WEIGHT PRETERM INFANTS: A META-ANALYSIS

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ABSTRACT

BACKGROUND: Nutritional status is crucial in neonatal survival, especially among the Very Low Birthweight (VLBW) preterm infants. They have low nutrient reserves with increased metabolic needs and immature gut system. Several studies have proven the efficacy of medium-chain triglycerides (MCT) as good source of calories among preterm infants. However, such is not commercially available. Virgin coconut oil (VCO) has the most concentrated content of MCTs, hence a possible source of MCT.

OBJECTIVES: This review aims to determine the efficacy of VCO-supplementation to milk feeding in augmenting weight gain among very low birthweight preterm infants.

METHODS: Pubmed (1975- September 2016), Cochrane Central Register of Controlled Trials (The Cochrane Library, September 2016), HERDIN (1966-September 2016), Google Scholar (September 2016), and https://clinicaltrials.gov (last searched September 2016) were thoroughly searched. Manual search in reference and citation lists of the eligible studies, and list of abstracts from the Philippine Pediatric Society was also reviewed. Only randomized controlled trials comparing VCO-supplemented milk versus standard care in weight gain among very low birthweight preterm infants were included. The author reviewed each study's quality and extracted data on weight gain. Weighted mean differences with 95% confidence intervals were reported. Risk of biases among studies were also evaluated.

RESULTS: Three randomized controlled trials involving 290 infants were included. All trials were of good quality with relatively low heterogeneity (39%), and low risk of biases. Overall, infants receiving VCO-supplemented milk feeding had statistically significant weight gain compared to those given non-fortified milk (Mean difference 5.31, 95% CI: 3.83 to 11.93).

CONCLUSIONS: Virgin coconut oil is effective in augmenting weight gain among very low birthweight preterm infants.

RECOMMENDATIONS: Small trials were used in this review, and a single multicenter randomized controlled trial would be ideal to further establish these findings.

KEYWORDS: "virgin coconut oil," "coconut oil," "medium chain triglyceride," "preterm," "very low birthweight," "weight gain"

INTRODUCTION

Nutritional status is a crucial element in neonatal survival, especially among the Very Low Birthweight (VLBW) preterm infants. Due to their prematurity, these infants are at high risk for the development of overwhelming infections and serious medical complications during their stay in the hospital. For this reason, it is of utmost importance that aggressive nutritional management be rendered beginning at birth.

Breastfeeding and human breast milk remains the gold standard of nutrient source for

all infants, including the VLBW preterm. Unfortunately, preterm human milk has been found inadequate for the special demands of the preterm infants, hence, the advent of milk supplements. Milk supplements may be in the form of protein, carbohydrate, fats, or a combination of these. Among these, fats provide the highest energy density, especially when given in the form of medium chain triglycerides. Medium chain triglycerides (MCTs) are notably advantageous among the preterm infants as these are readily digested, absorbed, and utilized in spite of the relative pancreatic insufficiency and gut immaturity of these patients. However, MCTs are not readily available in the Philippines, such that the use of virgin coconut oil as food supplement has gained popularity in its stead. Virgin coconut oil (VCO) is found to be the richest natural source of MCT, comprising of 48% lauric acid. This saturated fatty acid is believed to be responsible for most of its medical uses, including antimicrobial effects. Few studies on the use of VCO in weight augmentation among children had been done in the country, and all showed promising results.

Nutritional buildup among VLBW preterm infants is a primary concern among pediatricians. With the previous studies on MCTs and its alternative, VCO, revealing promising results, proving that it is effective in augmenting weight gain among this specialized subgroup of patients would greatly impact the practice of neonatal care in this country. Moreover, VCO is readily available and affordable in the Philippines. Further evidence on its efficacy could justify its use and applicability in the nutritional management of preterm infants.

Nutrition is a vital aspect in the care and management of neonates, particularly among preterm infants. Infants born premature are characterized with low nutrient reserves in a state of elevated metabolic rates, high evaporative loss, and immature gastrointestinal systems.[1-2] Such characteristics put these infants at high risk for nutritional compromise and its complications, that early and aggressive nutritional intervention is deemed synergistic to their survival.[1]

It is a standard practice in neonatal care to initiate parenteral nutrition in the first days of life among low birthweight and very low birthweight infants. This is to achieve the required caloric intake to prevent protein catabolism, while promoting growth and development comparable with intrauterine growth of a fetus of the same gestational age. Although replication of intrauterine growth is difficult to attain, the American Academy of Pediatrics recommend a weight gain of 15-20g/kg/day, an increase of 1cm/week in length, and 0.5-1cm/week in head circumference as goals for adequacy in nutrition.[1,2,4]

On the other hand, initiation of enteral feeding in the earliest possible time is crucial in the preservation of the structural and functional integrity of the gastrointestinal tract. However, rapid advancement of enteral feeding among very low birthweight preterm infants poses a risk for the development of necrotizing enterocolitis (NEC). Hence, cautious trophic feeding is initially recommended, a technique found to result in better feeding tolerance, improved levels of gut hormones, and in turn facilitating early progression to full enteral feedings.[1]

Despite recent advancements in milk formulation, human breast milk remains the gold

standard source of nutrition among term and preterm infants.[1,4] It provides both nutritional and immunologic benefits to the growing child, which no other milk formula could replicate.[1,2] However, nutrient levels in preterm human milk remain below the recommended levels, with varying composition through time. For these reasons, preterm human milk is usually supplemented with human milk fortifier (HMF), which increases its protein, energy and mineral content. Aside from HMF, other oral supplements may be given with varying caloric densities and inherent benefits and caveats.[1] These include supplemental protein, fat, carbohydrates or a combination of these. Studies have shown that increasing the protein content of the milk would result to greater, if not the greatest, increments in weight and length among VLBW and ELBW infants, even approximating their reference intrauterine anthropometrics after four weeks.[5, 6] However, high protein intake would result to positive nitrogen balance and elevated renal osmotic load, which may have deleterious neurologic and renal seqeuela among preterm infants. Another means of enhancing caloric value of infant feeding is the use of carbohydrate supplements.[1,2] However, due to the low disaccharidase levels in preterm infants, carbohydrate load of more than 50% of the dietary intake would result to gastrointestinal upset such as flatulence, colic, and diarrhea.[1]

Fats have the highest energy density among the three, with low osmolarity and rapid absorption. It comprises 40-50% of calories in human milk or formula. Fats are generally provided as a mixture of long chain triglycerides (LCT) and medium-chain triglycerides (MCT). LCT is a good source of polyunsaturated fatty acids and essential fatty acids, which make up 75-80% of all fatty acids in human milk. However, due to the relative pancreatic insufficiency and decreased bile salt excretion in early life, absorption of LCTs are impaired in this subset of the population. On the other hand, MCTs are readily absorbed even with gut immaturity. This is due to the presence of lingual and gastric lipases which hydrolyze MCTs to free fatty acids, allowing direct absorption, transport and cellular utilization without the need of micelle formation, chylomicrons, and carnitine.[1,2,7] It is for this reason that MCT supplementation in preterm milk holds great promise.

Several studies have been done in the past five decades on the use of MCTs as milk supplement for augmenting weight gain among preterm infants, albeit with conflicting results. Most studies would show incremental weight with MCT, however, not all would reach statistical significance.[5,8-13] A meta-analysis was done in 2008 which compared the effect of high-MCT with low-MCT formula on short-term weight gain among healthy VLBW preterm infants. This included eight randomized controlled trials with an average study duration of one week of full enteral feeds. However, results of this review revealed that there was no significant difference in the short-term growth parameters between high and low MCT formula.[15] On the other hand, a local study done in 1999 at the Philippine General Hospital revealed positive results in weight augmentation, with shortened hospital stay among preterm LBW infants supplemented with MCT.[14] The controversy surrounding the evidence on its efficacy for weight enhancement among preterm infants hinders its niche in standard management of neonatal nutrition. But different institutions consider it as a good option, hence, its continued use. However, MCTs are not commercially available in our country. Nevertheless, an alternative source of MCT in the form of coconut oil is of abundance in the Philippines.

Virgin coconut oil is the most concentrated natural source of medium chain fatty acid, which comprises nearly two-thirds of its saturated fat content. The main fatty acids in

coconut oil are lauric acid (48%), capric acid (7%), and caprylic acid (8%). Its high lauric acid content is said to be responsible for majority of its health benefits.[16-18] In vitro studies revealed conversion of lauric acid to monolaurin in the small intestines, demonstrating antibacterial, antiviral, and antifungal properties.[18] In a study done in India in 1992, results concluded that VCO as source of MCT supplementation in preterm milk was effective in augmenting weight gain among VLBW infants.[7] In the recent years, few researches in the Philippines had been done on the efficacy of VCO-supplementation in improving nutritional status of both VLBW preterm infants, and school-aged children. All studies revealed positive incremental weight in VCO-supplemented group versus the control group, with greater significance found among VLBW preterm infants.[19-26] Moreover, VCO was also found to shorten duration of hospital stay by decreasing the time to reaching the discharge weight, thereby decreasing the chance to develop nosocomial infections.[19,26] However, similar to the international studies on MCT-supplemented milk, results were also inconsistent, hence, this review was conducted.

The general objective of this study was to determine, by meta-analysis, the efficacy of virgin coconut oil supplemented milk feeding in augmenting weight gain among very low birth weight preterm infants.

METHODOLOGY

This meta-analysis only included randomized controlled trials (RCTs) of very low birthweight infants weighing ≤1500 grams assigned to virgin coconut oil (VCO)-supplemented breast milk or formula versus placebo or standard care. The studies included infants born less than 37 weeks with a birth weight of less than or equal to 1,500 grams, who were able to tolerate enteral feeding. Trials which included infants with co-morbid conditions such as congenital anomalies, inborn error of metabolism, and those who underwent surgical procedures, were excluded from this review. The studies included compared virgin coconut oil supplementation in preterm milk formula or breast milk to placebo or to standard care. Trials which made use of other fortifiers together with coconut oil or compared VCO supplemented milk with other weight gain enhancers were excluded. This review only measured the difference in weight gain between those who received VCO-supplemented milk versus those infants who received standard care.

The study made use of thorough literature review via the internet on available publicly accessible scientific journal databases such as PUBMED (1975- September 2016), Cochrane Central Register of Controlled Trials (The Cochrane Library, September 2016), HERDIN (1966-September 2016), Google Scholar (September 2016), and on-going trials in https://clinicaltrials.gov (last searched September 2016). Using the keywords "virgin coconut oil," "coconut oil," "medium chain triglyceride," "preterm," "premature," "very low birthweight," and "weight gain," a thorough literature search was performed. Manual search in the reference and citation lists of the eligible studies, and list of abstracts from the Philippine Pediatric Society was also conducted to look for other relevant unpublished studies.

The review author (ADB) and a research assistant used the titles and abstracts to already exclude trials which clearly did not meet our inclusion criteria. The common reasons encountered for exclusion of the articles from the electronic search were: non-human studies, the non-use of virgin coconut oil; measurement of outcomes which did not include weight gain.

Full articles were retrieved for further assessment if the abstracts indicated that there was a possibility that the study fulfilled the inclusion criteria. The two reviewers then independently selected the trials for inclusion in

the review from the list of potentially eligible trials. Seven potentially eligible papers were identified and reviewed. Four published and three unpublished articles were retrieved.

The author of this review was the one who contacted the trial authors for clarifications hence, was not blinded to their identity.

Two reviewers, (i.e. author and independent researcher) independently extracted the data and assessed trial quality. Missing data were requested from the trial authors.

A meta-analysis tool Review Manager version 5.3 downloaded from the Cochrane website was used in the meta-analysis. Data concerning the details of the trials included in the review using a specially designed data extraction form of "The Cochrane Collaboration" (Cochrane Library, 2009) were extracted. This included the following information:

- **General Information**: published/ unpublished, title, authors, year of publication;
- **Trial characteristics**: method of randomization and allocation concealment, blinding (participants, clinician, outcome assessor, loss of participants to follow up, intention to treat analysis;
- **Intervention**: dose, frequency of VCO supplementation and non supplementation with breast milk/expressed breast milk (EBM) or pre term milk formula
- **Participants characteristics**: preterm, very low birth weight, excluding those with congenital anomalies, inborn error of metabolism, and those who underwent surgical procedures
- **Outcomes**: weight increase (grams/day)
- **Results**: continuous data were expressed as weighted mean differences (WMD) and standard deviation (SD), use of intention to treat analysis.

Difference or conflicts in data extraction was resolved by discussion and consensus of the reviewers.

Using the Review Manager program, tests for heterogeneity and sensitivity were done. Quantification of the effect of heterogeneity were assessed by means of I^2.

Both positive and negative results were reported for all studies to be included. Each study to be included in the review was evaluated based on the following indicators of risk of bias:

- Adequate sequence generation
- Allocation concealment
- Blinding of participants, personnel, and assessors
- Incomplete data
- Selective outcome reporting

RESULTS

The search through PUBMED, Cochrane Library and Google Scholar only yielded two potential studies (Vaidya 1992; Singhania 1989), however, upon further assessment, only one study complied with the inclusion criteria for this review (Vaidya, 1992). The local search through the HERDIN yielded only two published pilot studies on VCO and infant weight gain (Amante 2005; Banzali, 2007). Unfortunately, both were excluded since the former study was subsequently completed and reported by Mantaring 2007, and the latter was an experimental, non-concurrent control study. Manual search in the reference and citation lists of the eligible studies, and list of abstracts from the Philippine Pediatric Society yielded three unpublished studies, two of which were included in this review (Mantaring 2007, Perez 2007).

A total of three studies were included in this review (Mantaring 2007, Perez 2007, Vaidya 1992). There was a total of 290 subjects who were included in this review. One hundred

and fifty-one (151) subjects were allocated the VCO supplemented milk feeding, while 139 subjects served as control, receiving non-fortified milk. The mean study size was 97 participants (range of 48 to 161 subjects). One study was published in 1992 and was conducted in India (Vaidya 1992), while the other two unpublished studies were conducted in the Philippine General Hospital (Mantaring 2007, Perez 2007). It was clarified with the authors that the studies had distinct and non-overlapping subjects.

The mean birthweight and age of gestation for the control and treatment groups in all trials had no significant difference. The mean birthweight of VCO group included in this review was 1304g (range of 1215.1±220.3 to 1399±46.7), while that in the control group was 1324g (range of 1238.8±29.9 to 1437±63.8). The mean age of gestation of the VCO group was 32.03 weeks (range of 31.8±2.2 to 32.21±1.15), while that in the control group was 32.34 weeks (range of 32.12±3.2 to 32.6±2.1).

All three studies included weight gain as either a primary or a secondary outcome, together with other anthropometric parameters. The study of Vaidya in 1992 made use of the brand "Parachute," by the Marico Industries Ltd, manufactured in Bombay, comprising of 43-49% MCT of total fat. Fortification of feeds in this study was done by adding 2 drops of VCO per 5 mL milk feeding. On the other hand, the two studies done locally made use of the brand "Oleum" whose composition had been documented by the Philippine Institute of Pure and Applied Chemistry[27]. The dose for both studies was 0.5 ml per ounce of milk given.

There were four studies that were excluded from this review. The study of Amante 2005 was a pilot study which was eventually completed and reported by Mantaring in 2007, which was the one included in the review. Another study was done in the Philippine Children's Medical Center in 2005 (Banzali 2005) was also excluded since it was an experimental non-concurrent study. The control group used in the trial was a cohort of infants admitted a year prior to the treatment group. Another local study done in The Medical City (Mendoza 2007) was also excluded since the comparator used was karo syrup. An earlier study in 1989 (Singhania) was also excluded as it used a combination of virgin coconut oil and sugar as the intervention, and included infants weighing up to 1750g as its subjects.

Randomization

All three trials were randomized controlled trials which made use of computer generated randomization software or the table of random numbers. However, the study of Vaidya in 1992 failed to elaborate on the exact method of randomization applied. There is an overall low risk of selection bias.

Allocation

The two local studies reported allocation concealment with the use of sealed, opaque brown envelopes. However, in the study done by Vaidya, the risk was unclear as there was no mention of the allocation method applied. Nevertheless, the baseline characteristics of the study subjects in both groups were not statistically significant, hence, it may be prudent to assume that allocation bias is generally low among these trials.

Blinding

The two local studies specified blinding of the physicians and outcome assessors during the study period. However, no blinding method was mentioned in the study done by Vaidya. Regardless of the unclear risk, the author did not consider such to greatly impact the risk for performance or detection bias.

Incomplete outcome data

In the study of Mantaring, 40 subjects who developed sepsis or died were excluded in the analysis of weight gain as the authors considered the presence of sepsis to have a "large influence on growth." The study of Vaidya excluded 5 subjects who died shortly after enrollment to the study, with one infant developing necrotizing enterocolitis (NEC). The reviewers agreed with the exclusion of these subjects from the trials as any comorbidity such as sepsis, NEC, and subsequent death may be a potential source of bias in data analysis.

Selective Reporting

Both significant and non-significant results were reported by the studies.

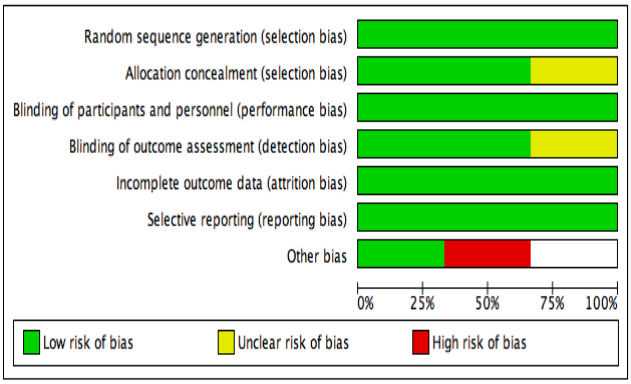

Figure 1. Risk of Bias graph: Review authors' judgments about each risk of bias item presented as percentages across all included studies.

Effects of Interventions

The three trials included in the review consistently revealed an increasing trend in the weight of the infants given VCO-supplemented milk feeding. In the study of Mantaring 2007 and Vaidya 1992, mean weight gain between groups were statistically significant, favoring VCO-fortified milk feeding. However, the study by Perez in 2007 did not reach statistical significance, albeit, the trend also favored VCO-supplementation. Combination of the three trial results revealed statistically significant difference (Mean difference 5.31, 95% CI: 3.83 to 11.93) in the positive effect of virgin coconut oil in augmenting weight gain among very low birthweight preterm infants. Heterogeneity of the three trials was at 39% which may not be significant.

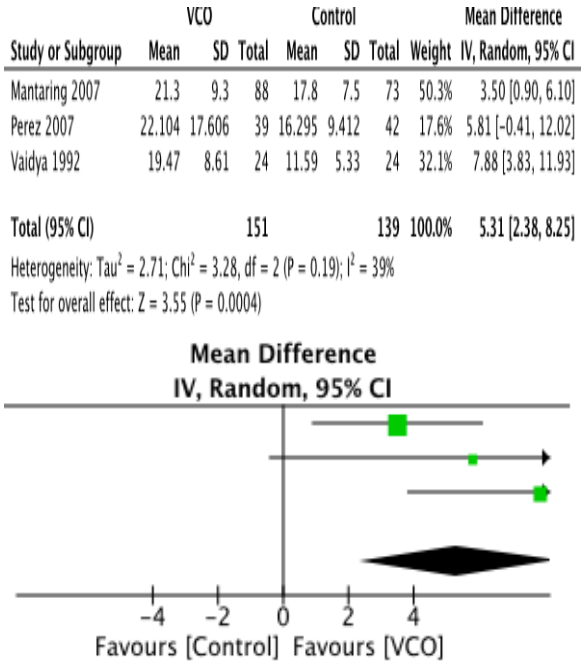

Figure 2. 1 Comparison of weight gain in VCO fortified milk group versus Control group, outcome: 1.1 Weight gain

DISCUSSION

Nutrition is a vital aspect in the care and management of neonates, particularly among preterm infants which comprise 10% of all babies born. Premature infants have low nutrient reserves with elevated metabolic rates, high evaporative loss, and immature gastrointestinal systems.[1-2] These put them at high risk for nutritional compromise and its complications, that early and aggressive nutritional intervention is crucial to their survival.[1]

Human breast milk remains the gold standard source of nutrition.[1,4] It provides both nutritional and immunologic benefits to the growing child, which no other milk formula

could replicate.[1,2] However, nutrient levels in preterm human milk remain below the recommended levels, with varying composition through time. For this reason, preterm milk is usually fortified with supplements to enhance its caloric density. Oral supplements include carbohydrate, protein and fats. Among these, fats have the highest energy density and is provided as a mixture of long chain- and medium-chain triglycerides. However due to the relative pancreatic insufficiency, decreased bile salt excretion and gut immaturity, MCTs are favored over LCTs. This is due to the presence of lingual and gastric lipases which hydrolyze MCTs to free fatty acids, allowing direct absorption, transport and cellular utilization without the need of micelle formation, chylomicrons, and carnitine.[1,2,7] Unfortunately, MCT oil is not available in the market, hence, alternative sources would be beneficial. Virgin coconut oil (VCO) contains two-thirds of its fat as medium chain triglycerides and is therefore, a good alternative source of MCT as milk supplement. Moreover, it is widely available and affordable in the Philippines.

Based on the results of this review, VCO supplementation of breastmilk or preterm milk augmented weight gain among very low birthweight preterm infants. The trials included in this review were of good quality. Although overall bias was relatively low, the trials were relatively small and two of which came from the same center. Therefore, the benefit of VCO in augmenting weight gain documented in this trial may have been spurious. A single, large, multicenter trial is ideal to accurately measure its benefit.

CONCLUSIONS

Implications for practice

There is statistically significant difference between VCO-supplemented milk feeding among preterm very low birthweight infants compared to those given non-fortified milk formula or breastmilk. Despite the small number of trials reviewed, the trend of positive weight gain was consistent in all trials, although one trial did not reach statistical significance. The results of this review provides supportive evidence in the practice of VCO supplementation among this special population.

Implications for future research

This review only involved three trials of small subject population. Further research ideally involving a single, multicenter randomized controlled trial would be highly recommended to further establish the benefit of VCO-supplementation in augmenting weight gain among preterm infants. Moreover, subgroup analyses based on different weight categories and age of gestation may provide a more comprehensive analysis of the role of VCO in weight augmentation among neonates.

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